American Journal of Medical Genetics 70:155–158 (1997)

Central Nervous System Anomalies in Seckel Syndrome: Report of a New Family and Review of the Literature

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Seckel syndrome (SS) is a rare, heterogeneous form of primordial dwarfism. The clinical delineation of this disorder has been inconsistent, using even Seckel's original criteria. As a result, probably fewer than one-third of reported cases are truly affected with SS. Among these, there have been only six familial cases, all of whom were born to normal parents, and in only one case has a detailed description of the central nervous system (CNS) anomalies been given.

We describe a family in which three of eight children were affected with SS. CNS anomalies seen in our patients included agenesis of the corpus callosum, a dysgenetic cerebral cortex, a large dorsal cerebral cyst, and pachygyria, suggesting an underlying neuronal migration disorder. The parents are first cousins, representing only the second instance of consanguinity, supporting an autosomal recessive mode of inheritance. Am. J. Med. Genet. 70:155–158, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: microcephalic; primordial; dwarfism; Seckel syndrome; autosomal recessive inheritance; pachygyria; neuronal migration disorder; agenesis of the corpus callosum

INTRODUCTION

First described in 1960, Seckel syndrome (SS) is a rare form of primordial dwarfism [Seckel, 1960]. Since the initial description, the clinical delineation of the entity has been inconsistent. In fact, of more than 60 cases reported between 1960 and the present, fewer than one-third appear to fulfill the criteria originally set forth by Seckel [Majewski and Goecke, 1982]. Among the generally accepted minimal criteria are: severe intrauterine and postnatal dwarfism; severe microcephaly with mental retardation; and facial anomalies, including a receding forehead and chin, large beaked nose, and large or bulging eyes [Seckel, 1960]. It is because of this latter characteristic that the term "bird headed" dwarfism was coined by Virchow and formerly applied to the condition.

To date, only six families with two or more children affected with SS have been reported [Aarons, 1964; Black, 1961; Cervenka et al., 1979; Harper et al., 1967; Krishna, 1994; Sauk et al., 1973]. In only one of these families has consanguinity been reported [Krishna et al., 1994]. Further, imaging studies of the central nervous system have only been described in two other reports [Sugio et al., 1993; Krishna et al., 1994]. We report on two sibs, born to a consanguinous Yemeni Arab couple, whose deceased sister had also been affected.

CLINICAL REPORTS

Patient 1

The proposita (VI-10 in Fig. 1) was seen neonatally because of microcephaly and minor anomalies. The 2.8 kg product of a full-term pregnancy complicated by maternal diabetes, she was delivered spontaneously from a breech presentation to a 43-year-old G8, P7006 woman. Because of her diabetes, the mother received insulin from the fifth month of gestation, and was hospitalized for two weeks during the third trimester because of poor glucose control. An amniocentesis, performed because of a small-for-dates biparietal diameter, showed a 46,XX fetal karyotype.

The parents are first cousins two generations removed (F = 1/32). The parents were born in Yemen.

Neonatally, the proposita was noted to be a strikingly microcephalic infant with length of 42.5 cm (<<5th centile), OFC of 25.5 cm (<<3rd centile), closed anterior and posterior fontanelles, and ridging of the lamdoidal sutures with a prominent occipital ridge. She also had a sloping forehead, prominent eyes with

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Received 6 May 1996; Accepted 20 September 1996

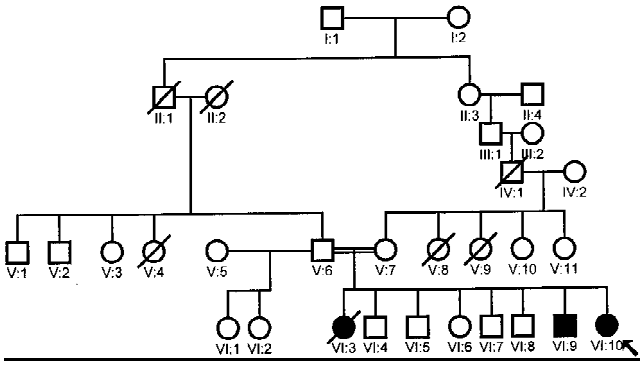

Fig. 1. Pedigree of family indicating consanguinity (F = 1/32).

normal interocular distances, a prominent, beaked nose, retruded mandible, and large, prominent ears with small lobules (Fig. 2).

The palate was high-arched, but intact. There were bilateral branched simian creases, clinodactyly of fifth fingers, and flexion contractures at the knees. The thighs appeared short and broad, suggesting the possibility of dysplasia or dislocation of the hips. On the basis of these findings, a diagnosis of SS was made.

Computed tomographic (CT) scan of the brain (Fig. 3) showed a dysgenetic cerebral cortex with pachygyria and a medially located left dorsal cyst, agenesis of corpus callosum and mild hypoplasia of the cerebellar vermis. At a resolution of 800 bands, chromosomes were normal.

Because of poor feeding, the proposita remained in the hospital for one month. When seen at 2 1/2 months, her length was 47 cm (<<5th centile), weight 3.3 kg (<5th centile), and OFC 27 cm (<<5th centile). She was an active and alert infant without spontaneous or social smile.

Patient 2

The older brother of the proposita (VII-9) was seen because of problems similar to those of his sister. The small-for-gestational-age product of his mother's seventh pregnancy, he measured 37.5 cm at birth (<<5th centile). His early course was marked by very poor feeding, poor growth, and marked delay in achieving psychomotor maturation.

This patient was evaluated by us at age 2 8/12. At that time, he was small and resembled his sister closely. Length was 68 cm (<<5th centile; 50th centile for 5-month-old), weight 7.3 kg (<<5th centile; 50th centile for 5-month-old), and OFC 32.5 cm (<<5th centile; 5th centile for a newborn). He also had a sloping forehead, prominent eyes, a large, beaked nose, and prominent ears (Fig. 4), simian creases, mild hypospadias, and talipes equinovarus of the right foot. Developmentally, he was greatly delayed; he was able to stand holding on, but neither walked independently nor took steps while holding on. He was nonverbal.

The family did not keep the appointment for magnetic resonance imaging of the head.

Patient 3

Individual VII-3 was the first child born to the parents of the proposita. She was of low birth weight (not

Fig. 2. Frontal and lateral view of the proposita's face showing typical craniofacial abnormalities.

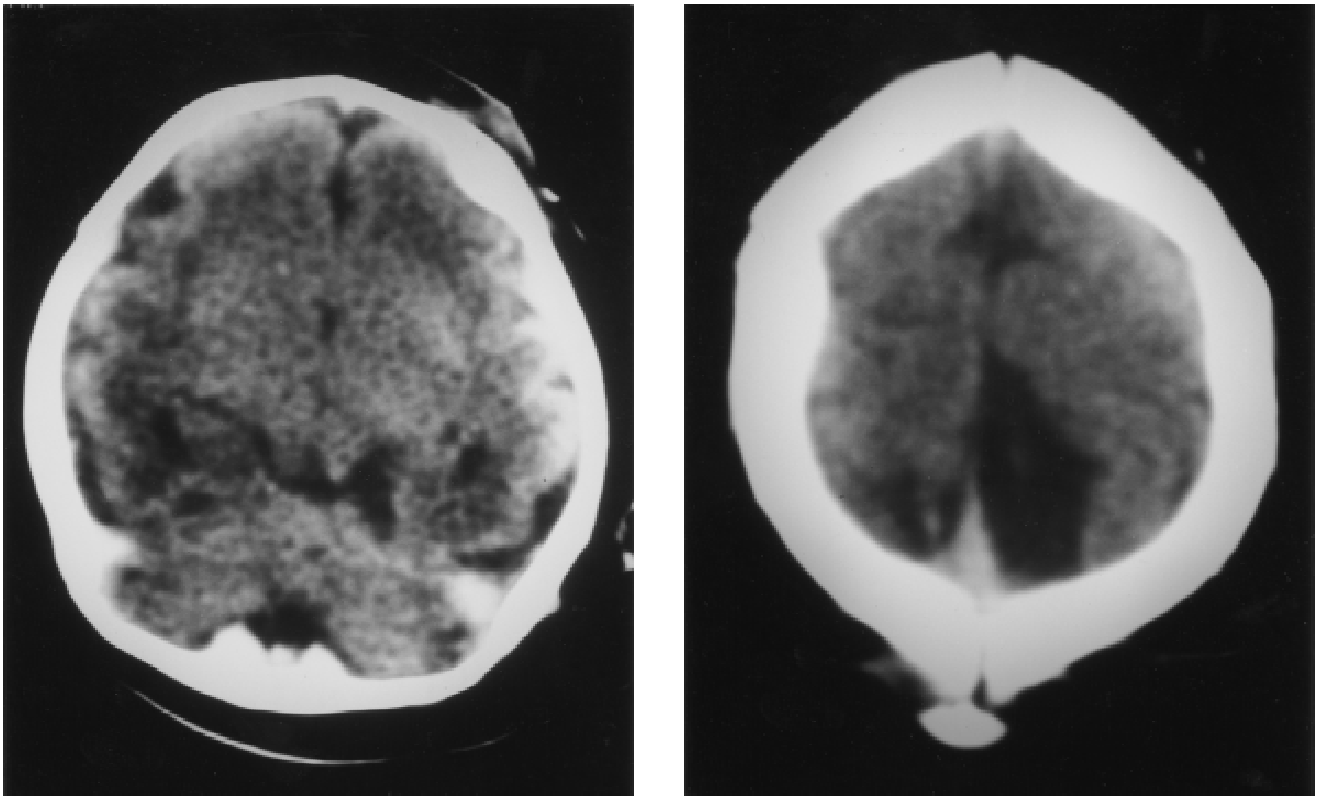

Fig. 3. CT scan of the head of the proposita, showing (left) the absence of the corpus callosum and pachygyria and (right), a large dorsal left-sided cerebral cyst.

Fig. 4. Frontal and lateral view of patient 2, showing resemblance to his younger sister.

TABLE I. Familial Cases of Seckel Syndrome

Author	Number of patients	Males	Females	Consanguinity in family
Present report	3	1	2	Yes
Black [1961]	2	0	2	No
Aarons [1964]	2	1	1	No
Harper et al. [1967]	2	1	1	No
Sauk et al. [1973]	4	1	3	No
Cervenka et al. [1979]	2	2	0	No
Krishna et al. [1994]	3	1	2	Yes
Total of 7 families	18	7	11	2

recorded), and greatly resembled the proposita and VII-9. Like her brother and sister, her early life was complicated by feeding difficulties, poor growth, and developmental delay. She died in Yemen at age 1, of unknown causes. She was never evaluated by a geneticist, no diagnosis was made, and no genetic counseling was provided for the family.

DISCUSSION

In the past, SS was an overdiagnosed condition. According to Gorlin et al. [1990], of the more than 60 cases reported, only 20 qualified as examples when the criteria first proposed by Seckel are considered. Our three patients all had proportionate postnatal growth deficiency, microcephaly, mental retardation, a characteristic facial appearance with sloping forehead, retruded mandible, and a prominent beaked nose, and, likely have SS.

According to the review of 17 cases reported by Majewski and Goecke [1982], all individuals with SS manifest intrauterine growth retardation with a mean birth weight of 1.543 kg (range 1.0 to 2.055 kg). Although, by report, our patients 2 and 3 fulfill this criterion, the proposita in this family, at 2.8 kg, was well above this range. An explanation for this discrepancy may be that the infant's mother developed gestational diabetes during the second trimester, a known cause of macrosomia.

Other anomalies seen in SS are clinodactyly of the fifth fingers (in 8/8 patients), hip "dysplasia" (5/9), dislocation of the head of the radius (3/6), cryptorchidism in three of four males, clitoromegaly in three of seven females, hirsutism (3/10) and enamel hypoplasia (6/10) [Majewski and Goecke, 1982]. Our patients 1 and 2 each had some of these anomalies.

This family represents the seventh instance of affected sibs born to normal parents (Table I). In addition, it is only the second family in which consanguinity has occurred, the other being the family reported by Krishna et al. [1994]. Interestingly, that family was also of Yemenite Arab background. These two families provide further evidence for autosomal recessive inheritance of SS.

A CT scan performed on Patient 1 neonatally showed agenesis of corpus callosum, hypoplasia of the cerebellar vermis, and a dysgenetic cerebrum with pachygyria and a medially located dorsal cyst. To our knowledge, this is only the third report of cerebral dysgenesis in patients with SS. CT and magnetic resonance scan findings in a 28-year-old affected woman (Patient 1 of Krishna et al., 1994) included a similarly dysgenetic appearance of the cerebral cortex with a midline interhemispheric cerebral cyst, poor convolutional markings, and a comparatively large basal ganglia and cerebellum. CT in a 2-month-old affected male [Patient 1 of Sugio et al., 1993] demonstrated hypoplastic cerebrum and cerebellum resulting in a largely empty intracranial space. These similarities suggest that neuronal migration abnormalities may be common in individuals with SS and that SS should be included with other neuronal migration disorders.

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